Status of the Claims

Claims 1-12 and 46 are pending. Applicants have amended claims 1-5, 10 and 11-12. As amended, claim 1 recites "cycling cells sensitive to the effects of high energy electromagnetic radiation," "high energy electromagnetic radiation," and " synchronizing at least 30% of said cells." Support for this amendment can be found throughout the specification and claims as originally filed, for example, at page 9, lines 3-5, page 8, line 26-27, and page 18, line 21, respectively. As amended, claim 10 recites "wherein said nucleic acid is fully encapsulated." Support for this amendment can be found throughout the specification and claims as originally filed, for example, at page 26, lines 21-25. Claims 2-5 and 12 have been amended solely to ensure proper antecedent basis. Thus, no new matter has been introduced by these amendments.

A version of the claims with markings to show changes to the claims are provided in Appendix A. All of the pending claims are provided in Appendix B for the Examiner's convenience.

In the present Office Action, the pending claims were rejected, in various combinations, under 35 U.S.C. § 112, first paragraph and under 35 U.S.C. § 103(a). Each of these rejections is addressed in turn below in the order set forth by the Examiner.

Rejection Under 35 U.S.C. § 112, first paragraph

Claims 1-12 and 46 were rejected under 35 U.S.C. §112, first paragraph as allegedly nonenabled. In making the rejection, the Examiner acknowledged that the specification ***is enabled*** for: cells sensitive to the effects of the electromagnetic radiation (*see,* page 3 of Office Action). The Examiner further acknowledged that the specification ***is enabled*** for synchronizing cells through the use of high energy electromagnetic radiation, such as x-rays and gamma rays (*see,* page 4 of Office Action). As set forth in M.P.E.P. § 2164:

> [a]ny analysis of whether a particular claim is supported by the disclosure in an application requires determination of whether that disclosure, when filed, contained sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention. *** ('The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation.'). A patent need not teach, and preferably omits, what is well known in the art. *In re Buchner,* 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991), *Hybridtech, Inc. v. Monoclonal Antibodies, Inc.,* 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986).

As explained in the Amendment filed October 10, 2000, the claims as originally filed are fully enabled by the specification as originally filed. In particular, Applicants respectfully submit that it would not require undue experimentation for one of skill in the art to determine whether a particular cell is sensitive to the effects of high energy electromagnetic radiation. However, in order to expedite prosecution, Applicants have amended claim 1 in accordance with the Examiner's suggestion. Specifically, claim 1 has been amended to recite "cycling cells sensitive to the effects of high energy electromagnetic radiation" and "high energy electromagnetic radiation." Applicants respectfully note that in light of Bolognia, *et al.* (provided with the Amendment filed October 10, 2000), high energy electromagnetic radiation also includes ultraviolet rays. Therefore, Applicants respectfully request withdrawal of this aspect of the rejection under 35 U.S.C. § 112, first paragraph.

The Examiner further alleges that claims 3-5 are not enabled because the specification allegedly lacks guidance or working examples that demonstrate that the cell can be synchronized in any other stage than G2/M. However, "[c]ompliance with the enablement requirement of 35 U.S.C. §112 first paragraph does not turn on whether an example is disclosed." (*See,* M.P.E.P. § 2164.02). Moreover, Applicants respectfully assert that it was known to those of skill in the art at the time the application was filed that electromagnetic radiation synchronizes cells at stages other than G2/M. For example, Rubin *et al.* (provided with the Amendment filed October 10, 2000) discloses that ultraviolet radiation synchronizes cells at ***either*** the G1 stage ***or*** the G1/S stage. Furthermore, Pellegata, *et al.* (provided with the Amendment filed October 10, 2000) discloses that gamma radiation synchronizes cells at ***either*** the G1/S stage ***or*** the G2/M stage. Thus, contrary to the Examiner's allegation, the same form of radiation ***does*** have the ability to synchronize cells at different stages in the cell cycle.

In view of the foregoing, Applicants respectfully submit that the claims, as originally filed, are fully enabled. Accordingly, Applicants urge the Examiner to withdraw the rejection under 35 U.S.C. § 112, first paragraph.

Rejections Under 35 U.S.C. § 103

The claims have been rejected, in various combinations, under 35 U.S.C. § 103(a) over a number of different references. Applicants respectfully traverse each of the § 103 obviousness rejections. As set forth in M.P.E.P. § 2143:

> [t]o establish a *prima facie* case of obviousness, three basic criteria must be met. *First*, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. *Second*, there must be a reasonable expectation of success. *Finally*, the prior art reference (or references when combined) must teach or suggest all the claim elements. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

All three elements set forth above must be present in order to establish a *prima facie* case of obviousness. As explained herein below in connection with each of the § 103(a) obviousness rejections, Applicants assert that a *prima facie* case of obviousness has not been established for at least the following reason: the cited references do not teach or suggest all of the claim limitations.

1. Rejection of claims 1-9, 11-12 and 46 over Yorifujji *et al.* in view of Spang-Thomsen *et al.*

Claims 1-9, 11-12, and 46 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Yorifujji *et al.* in view of Spang-Thomsen *et al.* In making this rejection, the Examiner alleges that Yorifuji *et al.* "demonstrate that through use of chemicals and electromagnetic radiation that synchronized cells are more efficiently transformed at different parts of the cell cycle," and that Spang-Thomsen *et al.* "teach the synchronization of *in vivo* analyzing various conditions for the optimization of synchronizing conditions." Applicants respectfully traverse.

Applicants respectfully submit that the teachings of Yorifuji *et al.* and Spang-Thomsen *et al.* have been mischaracterized. Yorifuji *et al.* disclose only that cells synchronized by two specific ***chemicals***, hydroxyurea and aphidicolin, exhibit greater transformation efficiency when transformed with linearized plasmid DNA via electroporation (*see,* page 201, col. 2). There is no hint or suggestion in Yorifuji *et al.* of using electromagnetic radiation to synchronize cells. Spang-Thomsen *et al.* is focused on the use of radiotherapy to induce tumor cell death, *i.e.*, the effect of x-irradiation on the proliferation kinetics of malignant melanoma cells. Spang-Thomsen *et al.* disclose

that exposure to x-rays induces ***partial*** synchronization of small fractions of malignant melanoma cells (*see*, abstract). Specifically, Spang-Thomsen *et al.* disclose that a maximum of 20% of malignant melanoma cells accumulated in the G2/M phases after exposure to x-rays, regardless of the dose or length of time post exposure to x-rays (*see,* Figure 1*)*. According to Spang-Thomsen *et al.*, "[i]t is questionable whether cell accumulation of this magnitude could be utilized in the design of fractionated radiotherapy to increase the treatment effect" (*see*, page 852, col. 2). There is no hint or suggestion in Spang-Thomsen *et al.* of transfecting cells after exposure to x-rays, or of increased transfection efficiency of cells after exposure to x-rays. Thus, one of skill in the art would not have been motivated to combine Yorifuji *et al.* with Spang-Thomsen *et al.* because Spang-Thomsen *et al.* teach away from using electromagnetic radiation to synchronize cycling cells in order to improve transfection efficiency as disclosed and claimed in the present invention. Moreover, even if the disclosures of Yorifuji *et al.* and Spang-Thomsen *et al.* were combined, they would not lead to the claimed invention because in contrast to Spang-Thomsen *et al.*, claim 1 recites "synchronizing ***at least*** 30% of said cells" (emphasis added).

Absent a teaching or suggestion to use electromagnetic radiation to synchronize at least 30% of cycling cells to improve transfection efficiency as disclosed and claimed in the present invention, the present invention is non-obvious and, thus, patentable. Accordingly, Applicants urge the Examiner to withdraw this rejection under 35 U.S.C. § 103(a).

2. Rejection of claim 10 over Yorifujji *et al.* in view of Spang-Thomsen *et al.*, further in view of Son *et al.*

Claim 10 stands rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Yorifujji *et al.* in view of Spang-Thomsen *et al.* as applied to claims 1-9, 11-12, and 46, and further in view of Son *et al.* In making the rejection, the Examiner alleges that Son *et al.* teach specifically how to transform a cell with a lipid-nucleic acid particle. Applicants respectfully traverse.

As explained above, one of skill in the art would not have had motivation to combine the teachings of Yorifujji *et al.* and Spang-Thomsen *et al.* Even if one of skill in the art were to combine Yorifuji *et al.* with Spang-Thomsen *et al*, the combination would not lead to the claimed invention because Spang-Thomsen *et al*, teach away from using electromagnetic radiation to synchronize cycling cells to improve transfection efficiency as disclosed and claimed in the present invention. Son *et al.* do not remedy the deficiencies of Yorifujji *et al.* and Spang-Thomsen *et al.*

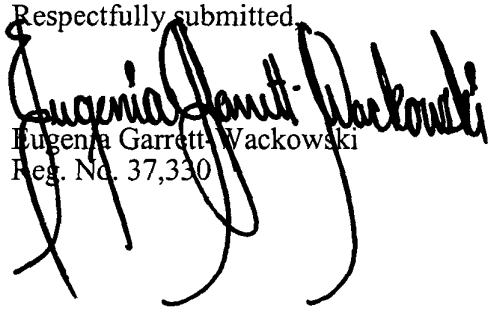
Son *et al.* disclose a DNA-liposome ***complex*** prepared by mixing DNA with liposomes (*see,* page 12669, col. 2). In the DNA-liposome complex of Son *et al.* the DNA is ***not*** fully encapsulated in the liposome. In contrast, to Son *et al.*, claim 20 recites "wherein said nucleic acid is fully encapsulated in a lipid-nucleic acid particle." The specification at page 26, lines 21-25 describes the encapsulated, nuclease resistant lipid-DNA particles as claimed in the present invention, and clearly they are different from the DNA-liposome complex of Son *et al.*

Absent a teaching or suggestion to use electromagnetic radiation to synchronize at least 30% of cycling cells to improve transfection efficiency of a nucleic acid fully encapsulated in a lipid nucleic acid particle, as disclosed and claimed in the present invention, the present invention is non-obvious and, thus, patentable. Accordingly, Applicants urge the Examiner to withdraw this rejection under 35 U.S.C. § 103(a).

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance and an action to that end is urged. If the Examiner believes a telephone conference would aid in the prosecution of this case in any way, please call the undersigned at 925-472-5000.

Respectfully submitted,



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APPENDIX A

VERSION WITH MARKINGS TO SHOW CHANGES MADE

1. (Twice Amended) A method of increasing the efficiency of transfection of cycling cells sensitive to high energy electromagnetic radiation, comprising:

synchronizing at least 30% of said cells at a first stage of the cell cycle by contacting said cells with high energy electromagnetic radiation, and

transfecting said cells at a second stage of the cell cycle within about one cell cycle of said first stage with a nucleic acid that encodes a desired gene product.

2. A method of claim 1 wherein said high energy electromagnetic radiation synchronizes cells at a stage of the cell cycle when the nuclear membrane is substantially degraded.

3. A method of claim 1 wherein said high energy electromagnetic radiation synchronizes cells at late S phase.

4. A method of claim 1 wherein said high energy electromagnetic radiation synchronizes cells at the G_2/M phase boundary.

5. A method of claim 1 wherein said high energy electromagnetic radiation synchronizes cells at a stage other than M phase, and the nucleic acid accumulates in cells that have cycled to the G_2/M phase boundary.

10. (Amended) A method of claim 1 wherein said nucleic acid is [part of a] fully encapsulated in a lipid-nucleic acid particle.

11. The method of claim 1 wherein said high energy electromagnetic radiation is a member selected from the group consisting of Gamma rays, X-rays, and ultraviolet rays[, infrared rays and microwaves].

12. The method of claim 11 wherein said high energy electromagnetic radiation is X-rays.